

REMARKS

Reconsideration and allowance of the application are respectfully requested in light of the foregoing amendments and the following remarks.

The present application relates to a method of treating or inhibiting the growth of cancer cells and associated diseases by administering certain substituted triazolopyrimidines.

Claims 1-95 are pending in the application. By the current amendments claims 23-66, 68-69 and 71-72 are canceled, and claims 1-14, 16-22, 70, 73-87 and 89-95 are amended. New claims 96 and 97 have been added.

The Examiner has rejected claims 1-21, 23-43, 45-65 and 67-94 under 35 USC 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons a-j apply:

- a. Claims 1, 23 and 45 appear as substantial duplicates of each other because they all recite the method of “inhibiting the growth of cancerous, tumorous cells” by administering “a substituted triazolopyrimidine derivative”. Although claims 23 and 45 recite some functional language, said language does not have patentable weight because it does not contribute to a structural change in the triazolopyrimidine derivative; and
- b. The Examiner has further rejected claims 2-22 and 67; claims 23-44 and 68; and claims 45-66 and 69 as dependent claims to substantial duplicate claims 1, 23 and 45 as having the same scope.

Applicants have canceled independent claims 23 and 45 and the claims which depend from them to remove the Examiner’s duplication rejection. Applicants thank the Examiner for pointing out the duplications of claims 1, 23 and 45. Because the rejection was on the basis of being duplicates, applicants believe that the present amendment does not affect the scope of the subject matter being claimed.

Applicants believe that claim 1 is patentable under 35 USC 112, second paragraph.

- c. The Examiner has rejected claims 2, 24, 46, 70-72 and 75 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention where instances of Broad/Narrow Range are presented, such as the following:
 - i. Broad limitation of “optionally substituted alkyl of 1-12 carbon atoms vs. narrow limitation of “haloalkyl of 1-10 carbon atoms” (e.g. see the definitions of R^a and R^b). In response, applicants have amended claims 2, 70 and 75 to remove instances of broad/narrow range especially in the definitions of R^a, R^b, R^c and R^d. Applicants believe the claims are clear and not indefinite and comply with 35 USC 112, second paragraph. Applicants respectfully request the Examiner to reconsider and withdraw the rejections and allow the claims.

- ii. Broad limitation of “heterocyclyl” vs. narrow limitation of “optionally substituted cycloalkyl of 3 to 8 carbon atoms in which one –CH₂– may also be replaced by –O–, –S–, or –NR’...” (e.g. see the definitions of R¹, R^a, R^b, R^c, and R^d). In response, applicants have amended the definitions of R¹, R^a, R^b, R^c, and R^d in claims 2, 70 and 75 to remove the broad/narrow range described by the Examiner. Applicants believe the claims are clear and not indefinite and comply with 35 USC 112, second paragraph. Applicants respectfully request the Examiner to reconsider and withdraw the rejections and allow the claims.
 - iii. Broad limitation of “heterocyclyl” vs. narrow limitation of “3- to 6-membered heterocyclyl ring, optionally ortho-fused...” (e.g., see the definition of R^a). In response, applicants have amended R^a and R^b in claims 2, 70 and 75 to remove the broad/narrow range phrase described by the Examiner. Applicants believe the claims are clear and not indefinite and comply with 35 USC 112, second paragraph. Applicants respectfully request the Examiner to reconsider and withdraw the rejections and allow the claims.
 - iv. Broad limitation of “aralkyloxy” vs. narrow limitation of “benzyloxy” (e.g., see the definition of R³). In response, applicants have amended R³ in claims 2, 70 and 75 to remove the broad/narrow range in particular in the definition of R³ as described by the Examiner. Applicants believe the claims are clear and not indefinite and comply with 35 USC 112, second paragraph. Applicants respectfully request the Examiner to reconsider and withdraw the rejections and allow the claims.
- d. The Examiner has rejected claims 4, 26, 48 and 77 for lack of antecedent basis because said claims recite (R) or (S) isomer, which is not recited in the claims they depend on. In response, applicants have amended claims 4 and 77 to include the language; “The method according to claim ... wherein R^a ~~and~~ or R^b ~~each~~ independently represent an optionally substituted alkyl moiety of 1 to 12 carbon atoms wherein said optionally substituted alkyl is represented by the moiety –C*H(R^e)(R^f) where R^e and R^f independently represent an optionally halo-substituted alkyl group of 1 to 12 carbon atoms where C* represents the (R) or (S) isomer or a pharmaceutically acceptable salt thereof is administered.” Claims 26 and 48 have been canceled. Applicants believe claims 4 and 77 as amended overcome the antecedent basis rejection and the claims are allowable.
- e. The Examiner has rejected claims 3-21, 25-43, 47-65, and 76-94 because they carry over limitations of claims 2, 24, 46 and 75. In response, applicants have amended claims 3-14, 16-21, 76-87, 89-94 to remove the carry over limitations from the definitions within R¹, R², R^a, R^b, R^c, R^d, R³, R⁴, and R[’]. Applicants believe the amended claims overcome the rejection and the claims are allowable.
- f. The Examiner has rejected claims 7, 11, 80 and 84 as being indefinite because they recite the broad limitation of “optionally substituted alkyl...” followed by the narrow limitation of “–CF₃”. Thus the resulting claims do not clearly set forth the metes and bounds of the patent protection desired. The applicants in response have amended

claims 7, 11, 80 and 84 to overcome the Examiners rejection and remove the narrow limitation of $-\text{CF}_3$. Upon further review, applicants have also amended R^4 in claims 2, 70 and 75 to remove $-\text{CF}_3$ as being a narrow limitation of "optionally substituted alkyl...". Applicants believe they have complied with the rejections by amending the claims and that the claims are allowable.

- g. The Examiner has rejected claims 17-21, 39-43, 61-65 and 90-94 as indefinite because they seem to recite an incomplete limitation of "wherein R^aR^b are optionally taken together with the nitrogen to which each is attached". Applicants have amended claims 17-18 and 91 to amend the incomplete limitation as described by the Examiner. As amended, " $-\text{NR}^a\text{R}^b$ wherein R^a and R^b when taken together with the nitrogen to which each is attached form an optionally.....", applicants believe the phrase is clear and the claims comply with 35 USC 112, second paragraph. Applicants have amended claims 18-21, 90 and 92 by removing the phrase "wherein R^aR^b are optionally taken together with the nitrogen to which each is attached" described by the Examiner. Applicants believe the claims are clear and not indefinite and comply with 35 USC 112, second paragraph and that the claims are allowable.
- h. The Examiner has rejected claims 20, 21, 42, 43, 64, 65, 93 and 94 as being indefinite for reciting the broad limitation of " $-\text{NR}^a\text{R}^b$ " followed by the narrow limitation of individual functional groups and rings such as: $-\text{N}(\text{C}_2\text{H}_5)_2$, $-\text{N}-\text{CH}(\text{CH}_3)_2$, $-(\text{N}-\text{piperidiny})-\text{CH}_3$ etc. Thus the resulting claims do not clearly set forth the metes and bounds of the patent protection desired. In response, applicants have amended claims 20-21 and 93-94 by removing the broad limitation " $-\text{NR}^a\text{R}^b$" cited by the Examiner. Claims 42, 43, 64 and 65 have been canceled. Applicants believe they have complied with 35 USC 112, second paragraph and the claims are allowable.
- i. The Examiner has rejected claims 70, 71 and 72 as substantial duplicates because they recite pharmaceutical compositions with different intended uses; however, intended uses do not have patentable weight. The applicants have amended claim 70 to include the phrase "and a pharmaceutically acceptable carrier.". Support for the amended phrase may be found in the specification on page 74, lines 18-26. Further, applicants have amended claims 70, and canceled claims 71 and 72. Therefore, the claims are no longer substantial duplicates. Claim 70 as amended is: "A pharmaceutical composition comprising and an effective amount.....or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier". The phrase "for treating or inhibiting the growth of cancerous tumour cells and associated diseases in a mammal in need thereof" has been deleted from claim 70. Applicants believe that claim 70 as amended is no longer a duplicate of claims 71 and 72 and complies with 35 USC 112 second paragraph and therefore allowable as amended. Reconsideration is respectfully requested.
- j. The Examiner has rejected claims 73 and 74 which recite "a method for the treatment or prevention of multiple drug resistance (MDR)..." which is unclear as to the disorders being treated. Also, it is not clear what resists what. In response the applicants have amended claim 73 to: "A method for the treatment or prevention of cancerous tumor cells that express multiple drug resistance (MDR)..." Applicants believe that the claim is now clear and that the disorders being treated are cancers. Support for the amending language can be found throughout the document and in

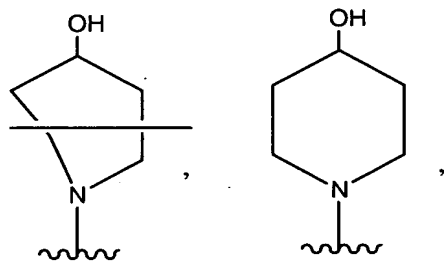
particular on pages 97-99. Applicants believe that the amended claim complies with 35 USC 112 second paragraph. Reconsideration is respectfully requested.

Claims 1-3, 6-8, 11, 12, 15, 23-25, 28-30, 33, 34, 37, 45-47, 50-52, 55, 56, 59 and 67-72 have been rejected under 35 USC 102(b) as being anticipated by Suiko et. al. (Agric. Biol. Chem., 41(10), 1977, pp 2047-2053. Disclosed are the following substitutions with regard to Formula I; R^1 is alkyl or hydroxy; R^2 is H, halogen or alkoxy carbonyl of 2 carbon atoms; R^3 is hydrogen or alkyl and R^4 is H. Applicants have amended claims 1, 2, 70 and 75 to include the proviso; R^1 is unsubstituted alkyl or hydroxy, R^3 is H or unsubstituted alkyl, R^4 is H and R^2 is not halogen or alkoxy carbonyl of 2 carbon atoms. It is therefore submitted that the rejection under Section 102 (b) over the Suiko reference may properly be withdrawn.

The Examiner has objected to claim 95 as being dependent upon a rejected base claim and would be allowable if rewritten in independent form including all the limitations of the base claim and intervening claims.

Applicants thank the Examiner for his statement that claim 95 would be allowable if rewritten in independent form including all of the limitations of the base claim and intervening claims. Applicants have amended claims 75-87 and 89-94 and believe that amended claims and original claim 88 are allowable and therefore believe that it is unnecessary to amend claim 95 to make it independent at this time.

Applicants have further amended claims 20, and 93 to correct a typographical error in a structure which appears in each claim. The portion of each claim which was amended is shown below. Support for the corrected structure is present on pages 34 and 40 of the specification and in claims 21, 42, 43, 64, 65, 94, as originally filed.



Applicants have amended the specification and added new claims 96 and 97 to the species 5-chloro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine. Both Example 169 and Example 170 are listed as the (1R) isomer. Applicants knew at the time of filing from the known chemical structures and the pharmacological test results that Example 133 was the racemic mixture, Example 169 was the (1R) and Example 170 was the (1S) isomer, 5-chloro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine. However, not recognizing

the typographical error of (1R) for (1S) the incorrect name became a repetitive error throughout the document as further seen on page 60 lines 7-11, claim 22, page 217, lines 7-11, and claim 95, page 394, lines 1-5.

Support for the amendment may be found in Tables 1, 2, 3 and 17 where the pharmacological test results support the difference between Examples 169 and 170. One of ordinary skill in the art would understand that these were different compounds. Based on the test results given for Example 170 and the compound disclosed in Example 133, together with the statement on page 70, lines 16-18, that the (S) isomers are compounds of the invention, applicants believe the amendments are supported.

In addition, synthetic methods to prepare Example 170 are described and, incorporated by reference, in U.S. Patent No. 5,986,135, column 12, lines 44-46 as Example 2. For the convenience of the Examiner, applicants note that the nomenclature described in Example 2 of U.S. Patent No. 5,986,135 is different from the nomenclature described herein for amended Example 170. However, the chemical structures are identical.

Applicants respectfully submit to the Examiner that the error in the chemical name of Example 170, in the specification and in claims 22 and 95 was only a typographical error and that the applicants knew the correct chemical structure and correct name before filing.

Applicants respectfully ask the Examiner to allow the corrections of the typographical error in the chemical name of Example 170, the specification and the claims as amended.

Applicants further refer the Examiner to the specification on page 60, lines 7-11 where lines 7-8 and 10-11 are the same text. The paragraph starting on line 10 and ending on line 11 has been amended to remove the R from the chemical name and replace with S.

Also in the specification on page 159, lines 2-3 are the same text as lines 29-30 on page 158. The paragraph starting on line 2 and ending on line 3 on page 159 has been amended to remove the R from the chemical name and replace with S.

In conclusion, applicants respectfully request that the Examiner enter the amendment, reconsider the rejections in light of the remarks herein, amendments to the claims and specification and allow the application. Favorable treatment is earnestly solicited.

Respectfully submitted,



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